between an antibody and a cell toxin, antigen binding antibody fragments [of antibodies] and active toxin fragments, or recombinantly produced antibodies, toxins, immunotoxins or fragments thereof, wherein the antibodies are directed to epitopes on the antigen EGP2 expressed by the gene GA733-2 and to epitopes on the antigen expressed by the [genes] MUC1 gene and the toxin is Pseudomonas exotoxin A.

3. (Amended) Method according to claim 1, characterized in that the used antibodies are MOC31 and 595A6, or antigen binding fragments thereof.

6. (Amended) Method according to claim 1, [characterized in that] wherein said exposure consists of administering the specific immunotoxins [are administered] in vivo.

14. (Amended) The method of claim 1, wherein said exposure consists of administering the immunotoxins [are administered] ex vivo.

REMARKS

No new matter has been added. The specification has been amended to correct typographical errors and to respect the proprietary nature of trademarks. Claims 1, 3, 6, and 14 have been amended to more clearly define the invention. Claims 1, 3, 6-8, 13, and 14 are pending in the application.

Applicants acknowledge the Examiners claim renumbering of misnumbered claim 13 as claim 14.

Specification

The specification has been amended to correct typographical errors and to respect the proprietary nature of trademarks.

Lack of Enablement Rejection

Claims 1, 3, and 6-8 have been rejected under 35 U.S.C. 112, first paragraph, because the specification allegedly does not enable one of skill in the art to make/use the invention commensurate in scope with the claims. Applicants respectfully traverse the rejection.

The Examiner stated that the specification does not reasonably provide enablement for an *in vivo* method. The Examiner further stated, "no one of skill in the art would accept the assertion that, based on the high specific activity of the disclosed immunotoxins *in vitro*, that administration of the mixture could be used for *in vivo* treatment of patients suffering from different types of carcinoma". In addition the Examiner stated, "[t]he specification does not provide teachings to establish effective dosages or methods of administration of antibodies specific for the two epitopes and no working examples are provided which would provide sufficient guidance to allow one skilled in the art to practice the above embodiments of the invention with a reasonable expectation of success".

Applicants respectfully assert that the specification does enable the claims because one skilled in the art would not have to perform undue experimentation to combine the present *in vitro* results with the use of immunotoxins and antibodies as was known in the prior art. The *in vitro* results demonstrated in the examples of the specification are the basis for *in vivo* use. It was known that the immunotoxins could cross-react with normal cells (Ref. 37. Pai et al., Appendix 3A, OBTAIN REFERENCE), thereby resulting in unwanted toxicity to normal cells. The present method overcomes this problem due to the higher specificity of the immunotoxins. That is, the specification demonstrates that the immunotoxins are not toxic for the normal cells in the body that are most vulnerable for toxicity, namely the stem cells in the blood and bone marrow, which otherwise limit cancer treatment. Thus, the specification illustrates that the present method would not result in toxicity to normal cells and tissues *in vivo*, such toxicity being a main problem with the *in vivo* administration of immunotoxins for therapeutic purposes.

Moreover, the general use of immunotoxins *in vivo* was known in the art (see enclosed literature, Appendices 3B and 3C), and it was known that immunotoxins could be specific for tumor cells, and could distribute to and concentrate in tumor tissue. For example, MOC 31 has been used in patients for immunoscintigraphy, showing in vivo specificity resulting in high concentrations in tumor cells compared to normal tissues (Kosterink et al, Appendix 2). Concentrations necessary for other immunotoxins were also available in the literature.

Thus, by combining the experimental evidence from *in vitro* experiments in the specification; the description of *in vivo* procedures presented in the last paragraph of page 12 to the third paragraph of page 13 of the specification; and learning from the prior art: a person with

knowledge in the art can perform the *in vivo* use of the present method without undue experimentation.

In addition, the Examiner stated, "the claims are drawn to the method, *in vivo* wherein CD-34+ cells or other immature/early progenitor cells are selected from the nucleated cells in peripheral blood. There is no teaching of how to accomplish this particular method *in vivo*".

Immunotoxins according to the claimed invention are used both to purge stem cell products *in vitro* and to be injected *in vivo* to kill tumor cells in different tissues. In the claimed method, CD-34+ cells are not selected *in vivo*; they are cells of a cell population upon which immunotoxins can be used according to the claimed invention.

Based on the above remarks, Applicant respectfully assert that the specification sufficiently enables one of skill in the art to make/use the claimed invention. Withdrawal of the rejection is respectfully requested.

Knowledge of concentration of the immunotoxin based on MOC 31 necessary for use in human tumors in mice and rats was in the possession of the inventors, as unpublished data. This may optionally be demonstrated in laboratory protocols. (IF YOU OR THE INVENTORS HAVE DATA SHOWING EFFECTIVE CONCENTRATIONS IN MICE AND RATS, WE SHOULD SUBMIT SUCH DATA TO THE EXAMINER IN THE FORM OF A DECLARATION).

Objection to Specification and Lack of Written Description Rejection

The specification was objected to and claim 3 was rejected under 35 U.S.C 112, first paragraph, as allegedly failing to provide an adequate written description of the invention and failing to provide an enabling disclosure. Applicants respectfully traverse the rejection.

The Examiner stated that the specification does not provide evidence that the claimed biological materials, monoclonal antibodies MOC31 and BM7, are (1) known and readily available to the public; (2) reproducible from a written description; or (3) deposited.

Applicants assert that these materials are available to the public and that one of skill in the art would be able to obtain such materials. MOC 31 is available from MCA Development b.v. (Appendix 4), and BM7 is available from S. Kaul, University of Heidelberg, Germany (See

methods section entitled, "Toxin, antibodies, and construction of immunotoxins" of Appendix 5, PLEASE PROVIDE ENTIRE REFERENCE). Also enclosed is a test report for BM7 (Accession No 95-014) from Anmed/Biosafe, Inc. (Appendix 6) and a copy of Investigational New Drug Application for MOC 31/PE and BM7/PE, required for acceptance to be tested in a planned phase I clinical trial (Appendix 7). One of skill in the art would be able to readily obtain the antibodies. The disclosure of the names of the antibodies is sufficient for one of skill in the art to obtain these publicly available materials, and therefore the materials are adequately described.

Withdrawal of the rejection is respectfully requested.

Indefiniteness Rejection

Claims 1, 3, 6-8, and 14 were rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse this rejection to the extent that it is maintained.

Claims 1, 3, 6-8, and 14 were rejected because claim 1 recites "other immature/early progenitor cells." The phrase "other immature/early progenitor cells from blood containing multipotent stem cells" has been deleted from claim 1.

Claims 1, 3, 6-8, and 14 were also rejected because claim 1 recites the phrase "characterized in". In claim 1, the phrase "characterized in that" ahs been replaced by "wherein" as suggested by the Examiner.

Claims 1, 3, 6-8, and 14 were also rejected because recites the phrase "fragments of antibodies and toxin". The phrase "fragments of antibodies and toxin" has been replaced with "antigen binding antibody fragments and active toxin fragments" as suggested by the Examiner.

Claims 1, 3, 6-8, and 14 were also rejected because claim 1 recited the phrase "by the genes MUC1." The phrase "by the genes MUC1" has been replaced with "expressed by the MUC1 gene" as suggested by the Examiner.

Claim 3 was also rejected because it recited the phrase "or fragments thereof". Claim 3 has been amended to recite "antigen binding fragments thereof" as suggested by the Examiner.

Claims 6, 7 and 13 were also rejected because term "administered" lacked antecedent basis in claim 1. Applicants assume that the Examiner intended to reject claim 13 rather than claim 13. Claims 6 and 14 have been amended to recite "wherein said exposure consists of administering" as suggested by the Examiner.

Claim 3 was also rejected because the designation of antibodies as MOC31 and BM7 rather that accession numbers allegedly renders the claim indefinite because different laboratories may use the same designations to define completely distinct hybridomas and antibodies. As indicated above the antibodies are readily and publicly available. As such applicants respectfully assert that one skilled in the art would find the designations MOC31 and BM7 clear and definite.

Claims 1, 3, 6-8, and 14 were also rejected for being written in improper Markush format. Claim 1 has been amended to be in proper Markush format as suggested by the Examiner.

In view of the above amendment and remarks, Applicants respectfully assert that the claims are clear and definite. Withdrawal of the rejection is respectfully requested.

Obviousness Rejection

Claims 1 and 14 were rejected under 35 U.S.C. 103 as allegedly being obvious over Lemoli et al in view of Brugger et al. Parry et al, Bjorn et al and US Patent No. 5,185,254. Applicants respectfully traverse the rejection.

None of the references alone or in combination teach or suggest the present invention, and one of skill in the art would not have looked to the cited references in attempting to derive the claimed invention.

Generally, immunotoxins described in the prior art, including ribosome inactivating proteins (RIPs), were not very toxic, and thus antibodies, which lacked specificity and cross reacted with normal cells, could be tolerated. The claimed method requires the use of PE, which is very toxic. As such, it is necessary that the toxin attack only malignant cells.

Lemoli et al is a typical example of the use of a weak toxin (RIP) and an antibody. In this case the antibody was directed to lymphoid associated antigens. The immunotoxin used by Lemoli et al kills both tumor cells and normal cells because the antigens are also expressed on normal cells. Additionally, the toxic protein used by Lemoli did not bind to the cells per se, and is much less toxic than PE. Because the presently claimed method requires the use of the toxic protein PE, which by itself might bind normal cells, the inventors could not risk killing haematopoetic stem cells. Therefore, it was of paramount importance to use highly specific antibodies binding two carcinoma cells. As such, nothing could be learned from Lemoli, and nothing in Lemoli suggested the claimed method.

Bjorn et al does not overcome the deficiencies of Lemoli et al. Bjorn et al disclose exclusively in vitro studies. Bjorn et al use PE with antibodies directed to antigens expressed on breast cancer cells. To study the efficiency of the method they run comparison with fibroblasts, which are not present in blood and bone marrow and are not very sensitive to immunotoxins and drugs. Thus, there is no suggestion in the reference as to how the present immunotoxins could be used *in vitro* or *in vivo* with cell populations comprising non-target cells vulnerable to the toxin. Thus, like Lemoli et al, Bjorn et al does not teach or suggest the present claimed method which addresses the crucial problem of killing relatively few target cells located among a high number of non-target cells that are very vulnerable to the used toxin.

Brugger et al does not overcome the deficiencies of Lemoli et al and Bjorn et al. Brugger's teaching is of course well known. It relates to the presence and mobilization of tumor and normal progenitor cells after chemotherapy. However, there is no suggestion in Brugger et al on how to kill malignant cells. Also, like Lemoli et al and Bjorn et al, Brugger et al does nothing to teach or suggest a method whereby a toxin is used to kill relatively few target cells located among a high number of non-target cells that are very vulnerable to the toxin.

Parry et al does not overcome the deficiencies of Lemoli et al, Bjorn et al, and Brugger et al. Parry et al refers to developmental regulation of major mucin glycoprotein expressed on the surface of mammary gland cells in mice. Mucin glycoprotein exists with highly differentiated degree of glycosylation. The reference provides no guidance as to how produce monoclonal antibodies to MUC1 with the high degree of specificity needed for the present claimed method. Nothing could be learned from this reference.

US Patent No. 5,185,254 does not overcome the deficiencies of Lemoli et al, Bjorn et al, Brugger et al, and Parry et al. US Patent No. 5,185,254 teaches a DNA sequence coding for an antigen recognized by GA 733.1 antibody, with many epitopes producing low specificity. When immunotoxins with a high degree of specificity and activity are necessary to kill more of the subpopulations of the carcinoma cells, as in the present claimed invention, it is not possible to simply replace an unspecific antibody as disclosed in the US Patent No. 5,185,254 with the present antibodies and conjugate them to toxins.

In summary, none of the cited references, alone or in combination teach or suggest the presently claimed method, which allows for killing of relatively few target cells located among a high number of non-target cells that are very vulnerable to the used toxin. Thus, the inventors

could not learn anything that could lead to the present invention from each of the cited references or combinations of thereof.

CONCLUSION

Applicants respectfully assert that the instant claims are in a condition for allowance, and earnestly solicit a notice to that effect.

If the Examiner has any questions regarding the foregoing, it is respectfully requested that he call the undersigned.

Respectfully Submitted,

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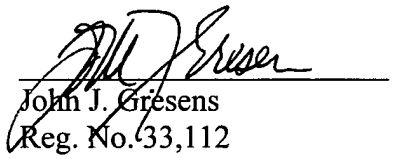

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